ORTEC INTERNATIONAL, INC
Audubon Business & Technology Center
3960 Broadway, New York, NY 10032

Composite Cultured Skin (CCS)

Instructions for Use

For Managing Surgical Wounds and Donor Sites Due to Hand Reconstruction in Recessive Dystrophic Epidermolysis Bullosa (RDEB) Patients As an Adjunct to Autografts and Surgical Flaps

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Instructions for Use

HUMANITARIAN DEVICE: Authorized by Federal Law for use in the treatment of patients with mitten hand deformities due to Recessive Dystrophic Epidermolysis Bullosa (RDEB). The effectiveness of this device for this use has not been demonstrated.

CAUTION: Federal Law restricts this device to sale by or on the order of a physician.

1. INDICATIONS FOR USE

Composite Cultured Skin (CCS) is indicated for use in patients with mitten hand deformities due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as an adjunct to standard autograft procedures (i.e., skin grafts and flaps) for covering wounds and donor sites created after the surgical release of hand contractures (i.e., "mitten" hand deformities).

CAUTION: This device should be used only by physicians (and properly licensed practitioners) trained in the surgical management of RDEB patients with mitten hand deformities, trained or experienced in the use of this device and prepared to provide patient monitoring.

2. PRODUCT DESCRIPTION

Composite Cultured Skin (CCS) is an aseptically processed wound dressing composed of a bovine collagen matrix (coated sponge) in which normal human allogeneic skin cells (epidermal keratinocytes and dermal fibroblasts) are cultured in two layers. Donor dermal fibroblasts are cultured on and within the porous sponge side of the collagen matrix and keratinocytes are cultured on the coated, non-porous side of the collagen matrix. CCS does not contain Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels or hair follicles.

CCS is manufactured under aseptic conditions using cells derived from human neonatal male foreskin tissue. The fibroblast and keratinocyte cells are tested for human viruses, retroviruses, bacteria, fungi, yeast, mycoplasma, karyology, isoenzymes, tumorigenicity, normal growth and morphology. The collagen matrix consists of a cross-linked collagen sponge, which is then coated on one side with a thin gel layer prepared from acid-soluble collagen. The collagen in this matrix is primarily Type I, derived from bovine corium. The final product is tested for morphology, cell viability, cell density, sterility, mycoplasma, and package integrity. Product manufacture also includes reagents derived from animal materials including bovine pituitary extract. All animal derived reagents are tested for: viruses, bacteria, fungi, yeast, and mycoplasma before use, and all bovine material is obtained from countries free of Bovine Spongiform Encephalopathy (BSE). The device measures approximately 6 cm x 6 cm (minimally 36 cm^2).

3. CONTRAINDICATIONS

- Composite Cultured Skin is contraindicated for use on clinically infected wounds (see Precautions).
- Composite Cultured Skin is contraindicated in patients with known allergies to bovine collagen.
- Composite Cultured Skin is contraindicated as the primary coverage of web spaces and palmar phalangial metacarpal joints during hand reconstructive surgery.

4. WARNINGS

- Allergic reactions to bovine collagen have been reported. Since bovine collagen is a component of Composite Cultured Skin, discontinue product use if a patient shows evidence of an immune reaction.

5. PRECAUTIONS

Caution: Composite Cultured Skin may contain trace amounts of penicillin, streptomycin, gentamicin, and fungizone (amphotericin B) used during cell processing. Avoid the use of this product in patients known to be allergic to these materials.

Caution: Allergic reactions to the components (see Section 8) of the shipping medium could occur. Patients should notify their physician of any symptoms of an allergic reaction. In clinical studies evaluating over 186 patients, no allergic reactions to the shipping medium were reported.

Caution: Composite Cultured Skin should be stored in its shipping container until ready for use.

Caution: Do not use cytotoxic agents with Composite Cultured Skin. Device exposure to mafenide acetate, silver sulfadiazine, polymyxin/nystatin, Providone-iodine solution or Dakin's Solution may also reduce Composite Cultured Skin's viability.

Caution: If clinical signs of infection (pain, edema, erythema, drainage, odor, warmth, and/or unexplained fever) are present or develop, do not apply Composite Cultured Skin until the infection is adequately treated and eradicated. All infections should be evaluated and treated according to standard clinical practice.

Caution: Composite Cultured Skin should be handled using aseptic technique and placed on a prepared wound bed, free of necrotic debris, within 30 minutes of removing sterile tray from sealed pouch.

Caution: The safety of CCS has not been evaluated in treating surgical wounds greater than 300 cm^2 and with more than 10 pieces of CCS within a three-week period. On average, the seven patients who underwent hand reconstruction surgery received 5 to 7 pieces of CCS over two weeks to cover wounds ranging in size from 120 to 300 cm^2.

Caution: The duration of CCS cells on wounds is unknown. The safety of CCS in two RDEB patients has been evaluated for 9 years. In vitro and in vivo, and clinical testing,

to date, has not revealed a tumorigenic potential of the CCS cells. However, the long term potential of skin cancers from these cells is unknown.

Caution: **DO NOT OPEN AND DO NOT USE** Composite Cultured Skin after the expiration date.

Caution: **DO NOT USE** Composite Cultured Skin if sterile package is opened or damaged.

Caution: **DO NOT** reuse, freeze, refrigerate, or sterilize after opening.

6. ADVERSE EVENTS

A. Epidermolysis Bullosa

The reported adverse events, which occurred in the studies evaluating CCS in RDEB patients with mitten hand deformities as an adjunct to standard autograft procedures and in the treatment of chronic ulcers in EB patients, at an incidence rate of greater that 1% are listed in Table 1. Because each patient in these studies received both CCS and standard care treatments on different wounds, the causality for systemic adverse events cannot be determined. Thus, the data below are presented with regard to the incidence of adverse events at treatment and control sites (i.e., local events on a per patient basis) and systemic adverse events.

Table 1 Adverse Events with an Incidence of Greater Than 1%

In Epidermolysis Bullosa Studies in U.S. and Australia

Adverse Event	Study Site Involvement		Systemic (n=19)
	CCS (n=19)	Control (n=24)*	
Fever	----------	----------	4 (21.0%)
Constipation	----------	----------	3 (15.7%)
Vomiting	----------	----------	3 (15.7%)
Pain	2 (10.5%)	0 (0.0%)	1 (5.2%)
Nausea	----------	----------	2 (10.5%)
Redness (total body)	----------	----------	1 (5.2%)
Erythema (non-study site)	----------	----------	1 (5.2%)
Edema (non-study site)	----------	----------	1 (5.2%)
Infection (Upper Respiratory)	----------	----------	1 (5.2%)
Squamous Cell Carcinoma (non-study site)	----------	----------	1 (5.2%)

* In the U.S. study involving 12 patients, there were 2 control sites per patient (acellular collagen sponge and standard care).

B. All CCS Treated Patients

The adverse effects observed during clinical evaluations of CCS patients with EB, as well as in other studies include a total of 8 deaths and 71 non-fatal serious adverse events in 186 patients. The non-fatal serious adverse events observed in patients treated with CCS are shown in Table 2. These adverse events were observed in seven clinical studies (including E.B.) and include a broader study population, some with systemic disorders, such as deep partial and full thickness burns. Of the 186 patients for which safety data are available, 82 (44%) had at least one adverse event reported. The adverse events with

the highest incidence levels were constipation 26 (13.9%), pain 24 (12.9%), fever 19 (10.2%), pruritis 14 (7.5%) and anemia 13 (6.2%). None of these adverse events (including the non-fatal serious adverse events) were judged by the treating investigators as definitely related to CCS application.

Table 2. Serious Adverse Events Observed in All Patients Treated with CCS (N=186).

SERIOUS ADVERSE EVENTS	# OF EVENTS
Reconstructive Surgeries	9
Contracture Release	9
Admission to Rehab Facility	5
Intubation	4
Sepsis	3
ARDS	3
Hypotension	3
Non-Healing Wound*	3
Infection	3
Autograft (Non-CCS Site)*	3
Renal Failure	2
Pneumothorax*	2
Pneumonia	2
Cellulitis	2
Leg Clots	1
Surgical Interventions:	-
Hip	2
Hernia Repair	1
Knee	1
Periodontal	1
Hand	1
Thoracotomy	1
Femoral Artery*	1
Infarction	1
Chest Pain	1
CHF	1
Minor Stroke	1
Seizure Disorder	1
Squamous Cell Carcinoma	1
Multi System Organ Failure	1
Necrosis to Musculature Around Femoral Artery*	1
Bleed at Femoral Artery*	1
TOTAL SERIOUS ADVERSE EVENTS	**71**

* One of these events in each of these categories is related to the control treatment.

7. CLINICAL EXPERIENCE

CLINICAL EXPERIENCE IN AUSTRALIA (Published in the British Journal of Plastic Surgery, 1998; 51, 608-613)

Hand Reconstructive Surgery

Surgical correction of the progressive hand syndactyly and flexion contractures in the recessive dystrophic epidermolysis bullosa population was carried out using Composite Cultured Skin (CCS) as a partial substitution for autografts and as a wound dressing for donor site coverage. From 1988 to 1994, a series of 15 operations to release hand contractures using CCS were performed on seven recessive dystrophic epidermolysis bullosa children.

CCS was used on the hand in combination with surgical flaps and autografts to cover open areas. After the surgical release of hand contractures, dorsal surgical flaps were used to cover a part of the web spaces and autografts were used to cover the palmar metacarpal phalangial areas with adjoining web spaces. CCS was then used to cover the open areas of the dorsum and fingers, and autografts were used to cover the remaining open areas of palmar surfaces. At the 7, 14, and 21-day postoperative dressing changes, CCS was reapplied to unepithelialized areas.

Long-term functional and quantitative assessment of the results of hand surgeries was based on the status of the adduction deformity of the thumb. The mobility of the thumb was used as a measurement of functional success (ability to "pinch"). Functional results of the treated hands were judged by the investigator to be good to excellent. In the Australian study, 58% of the wounds were covered with CCS, while 42% were covered with autografts and surgical flaps. CCS reduced substantially the need for autograft harvesting in these patients. The patients treated with CCS underwent additional surgical release of hand contractures after 2 to 10 years (See Table 3 below). The table illustrates the time between hand reconstruction surgeries for wounds covered with either autograft or autograft plus CCS. The number to the right of the surgical procedure reflects the time between that surgical procedure and the previous operation. The decision to re-operate was based on several factors including the severity of the disease, the patient's overall medical condition and the patient's compliance with physiotherapy of the hand.

Table 3 Time Between Surgeries

Pt ID#	Surgery #	Left Hand		Right Hand	
		Type of Surgery	Elapsed time between surgeries (months)	Type of Surgery	Elapsed time between surgeries (months)
1	1	Autograft	-	Autograft	-
	2	CCS + Autograft	17		
	3			CCS + Autograft	37
	-	Last Follow-Up	62*	Last Follow-Up	43*
2	1	Autograft	-	Autograft	-
	2	CCS + Autograft	53		
	3			CCS + Autograft	61
	4	CCS + Autograft	54		
	5			CCS + Autograft	52
	6	Autograft	70		
	-	Last Follow-Up	13*	Last Follow-Up	77*
3	1	CCS + Autograft	-		
	2			CCS + Autograft	-
	-	Last Follow-Up	83*	Last Follow-Up	75*
4	1	Autograft	-		
	2			Autograft	-
	3	Autograft	17		
	4	Autograft	46		
	5	Autograft	46	Autograft	102
	6	CCS + Autograft	36	CCS + Autograft	36
	7	CCS + Autograft	24		
	8			CCS + Autograft	49
	-	Last Follow-Up	121*	Last Follow-Up	96*
5	1	Autograft	-	Autograft	-
	2	Autograft	28	Autograft	28
	3	CCS + Autograft	65		
	-	Last Follow-Up	53*	Last Follow-Up	118*
6	1			CCS + Autograft	-
	-			Last Follow-Up	17*
7	1-10	Hand surgeries **	<12	Hand surgeries **	<12
	11	Autograft	-	Autograft	-
	12	Autograft	13		
	13			Autograft	15
	14	Cultured Keratinocytes***	24		
	15			CCS + Autograft	36
	16			CCS + Autograft	28
	-	Last Follow-Up	66*	Last Follow-Up	24*

* The time between last hand surgery and last follow up.

** Pt# 7 underwent 10 initial hand reconstructive surgeries over 7 years before he was referred to the Eisenberg-Llewelyn group. These surgeries did not include the use of autografts or CCS.

*** Recontractures of the hand after one year but no additional surgeries performed.

Donor Sites

The donor sites used to prepare autografts were also treated with CCS. In 13 surgeries, the CCS-treated donor sites healed in two weeks and in one surgery healed in three weeks. The long-term follow up of three patients has shown their donor sites to remain stable and free of blisters for six to ten years (1 and 2 patients, respectively). There was no incidence of delayed healing, infection or squamous cell carcinoma in any of the CCS-treated donor sites.

In addition, two patients had autografts harvested from previously CCS-treated areas and retreated with CCS. These donor areas had been treated with CCS two to four years earlier. Both donor sites yielded good quality autografts without shearing of the epidermis from the underlying dermis and healed without any complications. Biopsies from the CCS-treated donor sites were taken from two patients after 3 weeks and from one patient after 2 years to evaluate the histology of the healed skin. Histological results of these biopsies all showed fully formed epidermis on a regenerated neodermis.

CLINICAL INVESTIGATIONS IN THE UNITED STATES

Chronic Wounds in Patients with EB

A controlled randomized study of the effects of Composite Cultured Skin on the treatment of non-healing chronic wounds of patients with epidermolysis bullosa (Junctional and Dystrophic) enrolled a total of 12 patients. Ten of the twelve patients completed the study; the remaining two patients discontinued prematurely from the study. Of these two patients, one patient had a serious adverse event of squamous cell carcinoma, which the investigator considered to be a pre-existing condition, and not related to the study treatment. The other patient was lost to follow up.

In this within-patient controlled study, three non-healing chronic wounds in each patient were treated with either: 1) CCS, 2) the collagen sponge component of CCS or 3) standard of care. Reapplication of CCS during the first 4 weeks of the study was at the discretion of the investigator. The safety and efficacy assessments were made on study days 7, 14 and 21 as well as weeks 4, 8, 12 and 26. There were no incidences of wound infection, delayed wound healing, or cellulitis associated with the use of CCS reported in this study.

Immune Response:

Investigations in the United States, to date, have not revealed any significant clinical manifestations of product-related immune reactions. These clinical data include treatment of over 186 patients (including 12 EB patients). Sera drawn from patients in U.S. studies revealed no antibody responses to ***bovine Type I collagen***. Impact of device application on patients' humoral and cellular immune responses to the allogeneic human cellular components of CCS, i.e., keratinocytes and fibroblasts, such as HLA antigens or potential blood group antigens, has not yet been evaluated.

8. HOW SUPPLIED

A. Package Description

Composite Cultured Skin (CCS) measures approximately 6 cm x 6 cm (minimally 36 cm^2). A non-adherent, medical grade mesh (N-Terface® (Winfield Laboratories, Inc., Dallas, Texas)) is placed on both aspects of the device to protect the cells. One sheet is blue N-Terface®, which covers the fibroblast/dermal side of Composite Cultured Skin. The other sheet is white N-Terface®, which protects the keratinocyte/epidermal surface of Composite Cultured Skin. The device is packaged in a plastic tray with protein-free packaging medium containing HEPES buffered DMEM, L-Glutamine and MEM non-essential amino acids to maintain cell viability during storage and shipping.

The plastic tray is sealed within a peelable inner pouch to provide a sterile barrier against moisture and gas. The inner pouch is, in turn, sealed inside a heavier-gauge outer pouch that protects the inner pouch sterile barrier and the product against damage during shipment. The multi-stage packaged product is packed with pre-chilled gel packs and shipped to the destination in a padded and insulated shipping container that maintains a temperature of 11-19° C (for up to 72 hr.).

To maintain cell viability, Composite Cultured Skin is aseptically manufactured, but not terminally sterilized. CCS is shipped following a preliminary 48 hour incubation sterility test to confirm the absence of microbial growth. Final (14 day incubation) sterility test results are not available at the time of device application.

B. Storage

1. Composite Cultured Skin is to be stored in the original shipping container in which it was received. Do not store in refrigerator or freezer. The original shipping container maintains the correct storage temperature of 11 to 19°C.

2. Do not remove from original shipping container until ready to use.

C. Package Inspection

1. Visually inspect the Composite Cultured Skin clear packaging. The clear packaging should be intact. If the packaging is damaged, the Composite Cultured Skin device is not acceptable for patient application.
2. Visually inspect the medium in which the Composite Cultured Skin device is transported. The medium should not appear cloudy in color. Any cloudiness of the medium is an indicator the Composite Cultured Skin device is not acceptable for patient application.
3. Visually inspect packaging label. Check expiration date and time. Adhere strictly to expiration date and time guidelines.

9. DIRECTIONS FOR USE

A. Method of Application

General

1. Prepare the wound bed so that it is clean and free of necrotic material.
2. Open outer clear package of the Composite Cultured Skin device containing inner sterile pouch.
3. Dispense inner sterile pouch containing plastic tray onto the sterile field. Open pouch.
4. Place the tray on a sterile flat surface with the blue N-Terface® backing dermal side facing up.
5. To open the tray, stabilize the bottom tab while simultaneously lifting up on the top tab.
6. Using sterile noncrushing forceps, gently remove and discard the blue N-Terface® backing material.
7. With two sterile noncrushing forceps, grasp adjacent corners of the device in unison with the white N-Terface® backing material.
8. Position the device so that the white N-Terface® backing material (covering the epidermal surface) is facing up and away from the cleaned wound bed. Leave white N-Terface® in place to serve as the primary contact layer.
9. In this orientation, the dermal aspect of the device is in direct contact with the wound bed.
10. See specific indications for use below for further directions regarding outer dressings.

Donor Sites

1. The Composite Cultured Skin (CCS) device should be positioned so that there is a slight overlap (approximately 0.5 cm) onto intact skin. If more than one device is used to cover a wound surface, a slight overlapping of the edges of each Composite Cultured Skin device is recommended. Once placed on the wound bed, further manipulation of the Composite Cultured Skin device to improve positioning should be minimized, although it may be performed, as long as the device is grasped together with the white backing in place and moved in unison.
2. Cover the CCS device(s) with a nonadherent dressing and outer gauze wrap.
3. Allow overlying dressings to remain undisturbed for approximately 48 to 72 hours and then follow post application directions for care.

Hand Reconstructive Surgeries

1. After the surgical release of contractures, dorsal surgical flaps are used to cover a part of the web spaces and autografts are used to cover the palmar metacarpal phalangial areas with the adjoining web spaces. These areas need to be grafted with partial thickness autografts.
2. CCS is then used to cover open areas around the fingers and on the dorsum of the hand.
   a. When using CCS to cover the dorsal area, CCS may be cut into smaller pieces to fit the designated area. Using sterile scissors, cut through both the CCS and the N-Terface® backing material together as a single unit. Remaining unused parts of CCS should be discarded following guidelines for disposal of biological materials.
   b. When using CCS to cover fingers, CCS should be wrapped around each finger. After wrapping CCS, excess CCS should be cut leaving a slight overlap (approximately 0.5 cm) over CCS itself.
3. Cover the CCS device(s) with a nonadherent dressing and outer gauze wrap.
4. Allow overlying dressings to remain undisturbed for approximately 48 to 72 hours and then follow post application directions for care.

B. Post Application Directions of Care

Donor Sites

1. After Composite Cultured Skin has been applied to the affected areas as instructed in the directions for use, the donor site should be inspected by removing overlying nonadherent dressings at a minimum of every 48 to 72 hours.

   Note: The white N-Terface® backing lying directly on top of the Composite Cultured Skin should remain in place for 1 week.

2. The site should be inspected for any signs of redness, tenderness, itching, pain, or foul odor. The surrounding area may be gently cleansed with normal saline.
3. The site should be redressed with nonadherent dressings and an overlying gauze wrap.
4. After 1 week, the dressings should be removed and an attempt to gently peel back the white backing with forceps should be made.

   NOTE: The white backing may be adherent and may require soaking the area with normal saline to encourage loosening of the backing material. If portions of the backing remain adherent despite soaking, leave in place for approximately 24 to 48 hours and reattempt.

5. Once the white backing has been completely removed, gently cleanse the area with normal saline. If there are portions of the wound that remain unhealed, cover with nonadherent dressings and wrap with an overlying gauze wrap. Continue to assess healing of the area on a 24- to 48-hour basis.

6. Once the area has healed, caution should be taken so as to prevent any unnecessary trauma to the newly healed area, as newly healed skin may be fragile and susceptible to wound breakdown. Patients are instructed to care for the newly healed skin as directed by their physicians.
7. Patients are instructed to inspect the newly healed area daily for any of the following signs of breakdown: redness, tenderness, blistering, foul odor, drainage, or a moist, glistening appearance of the area. If any of these signs appear, the patient should notify their physician.

Hand Reconstructive Surgeries

1. The post-operative directions for hand reconstructive surgeries are similar to those for the treatment of donor sites (See steps Donor Sites B1-4).
2. At the one week post-operative dressing change, after removal of the white N-Terface® backing, all treated areas are to be examined. The CCS treated areas are to be examined for areas that have not started to epithelialize and the autografts are to be examined for areas where the autograft might not have taken.
3. Non-epithelialized areas and areas where the graft has not taken should be covered with CCS according to the standard directions for use. It should also be noted that areas previously covered with surgical flaps may now be treated with CCS to minimize the need for additional autografts.
4. After 7 additional days, if there are non-epithelialized areas, a third application of CCS may be performed.

10. PATIENT INFORMATION

Patients and parents should be counseled regarding the following information:

1. Basic information about patient's condition,
2. Basic information about Composite Cultured Skin,
3. How Composite Cultured Skin is used in hand reconstruction surgery and the treatment of donor sites, and
4. Post-operative care.

11. PEEL OFF LABEL

Remove the peel-off label from the CCS package label and place it in the patient's chart. This label bears the lot number and expiration date of the CCS.

Manufactured By: Ortec International, Inc.
3960 Broadway
New York, NY 10032

For more information, call (212) 740-6999.

In the case of an emergency, call pager number 1(800) 501-3554.

Date of Issuance: March xx, 2001 **[insert date of approved labeling]**

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Composite Cultured Skin (CCS)

Patient Information

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CAUTION: Federal Law restricts this device to sale by or on the order of a physician.

1. RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (RDEB)

Your doctor has diagnosed your or your child's condition as recessive dystrophic epidermolysis bullosa (RDEB). RDEB is inherited and is characterized by the development of blisters and erosions in the skin, and sometimes the mucous membranes after mild trauma. With this type of epidermolysis bullosa, blistering can affect nearly all skin surfaces, especially the fingers and toes. They can become immobile with recurrent scarring causing the fingers and the toes to fuse together.

Hand reconstructive surgery is one of the many surgeries performed to correct the complications related to inherited RDEB. In general, hand reconstruction improves a patient's ability to use their hands for a few years, (after which the surgery may be repeated). Hand reconstructive surgery is usually recommended when the disease has resulted in sufficient scarring of the hands and partial or complete loss of one or more web spaces in the hands. This deformity is commonly referred to as "mitten hand." If the disease is severe, patients with the "mitten hand" deformity may, over time, experience partial bone and muscle loss in the underlying digits. Surgery to correct the "mitten hand" deformities through hand reconstruction requires the release of the contractures (i.e., abnormal shortening of muscle or scar tissue).

The standard treatment for covering wounds on RDEB patients after hand reconstruction surgery includes non-adherent dressings or surgical alternatives such as autologous skin flaps and/or split thickness skin grafts. A skin graft or split-thickness autograft requires taking skin from an unaffected portion of the patient's body (usually the thigh or back) and grafting this skin to the surgical wound. The area from where the skin graft is taken is called a donor site. This wound also requires coverage with a wound dressing to prevent infection and promote healing.

2. INFORMATION ABOUT COMPOSITE CULTURED SKIN (CCS)

Composite Cultured Skin (CCS) is a wound dressing made with a sponge of cow collagen and two types of living human cells found in skin, (i.e., keratinocytes from the epidermis and fibroblasts from dermal tissue). CCS does not contain blood vessels, hair follicles, the cells which give skin color (i.e., melanocytes) or the skin's immune cells (i.e., Langerhans cells, macrophages or lymphocytes).

CCS is prepared with cells isolated from human neonatal foreskin tissue. These cells tested negative for human infectious agents. Making the product also requires animal-derived materials including bovine (cow) pituitary extract. All animal materials are also tested negative for infectious agents. All bovine material is purchased from countries free of Bovine Spongiform Encephalopathy (BSE; ***Mad Cow Disease***). Because the cells in Composite Cultured Skin are living, the device cannot be terminally sterilized. Instead, CCS is shipped after the device passes a preliminary sterility test.

3. WARNINGS AND PRECAUTIONS

As a patient and/or parent, you should be aware of the following warnings and precautions of CCS use:

- Composite Cultured Skin should not be used on infected wounds.
- Allergic reactions to collagen from cows have been reported. Since cow collagen is a component of Composite Cultured Skin, if you or the patient show evidence of an immune reaction (rash, swelling, redness), immediately tell your physician.
- This product may contain trace amounts of penicillin, streptomycin, gentamicin, and fungizone (amphotericin B) used during cell processing. If you have a known allergy to any of these antibiotics or you experience an allergic type reaction (rash, swelling, redness), immediately tell your physician.
- Product manufacturing includes reagents derived from animal materials. If you have a known allergy to any animal products, immediately tell your physician.
- Do not rub any medicines into the skin unless directed by your physician.
- If signs of infection (pain, swelling, redness, drainage, odor, warmth, and/or unexplained fever) develop, contact your physician immediately.
- The duration of CCS cells on a wound is unknown. CCS was found to be safe and did not show any potential to cause skin cancer on 2 RDEB patients that were followed for 9 years. *In vitro* (i.e., tests in culture dishes), animal, and human testing, to date, has not revealed a tumorigenic (***cancer producing***) potential of the cells contained in CCS. However, the long term potential of skin cancers from these cells is unknown.
- The safety of CCS has not been established for patients receiving greater than 10 applications.

SIDE EFFECTS:

A. Epidermolysis Bullosa

The adverse events, which occurred in EB patients, at an incidence rate of greater that 1% are listed in Table 1. Because each patient in these studies received both CCS and standard care treatments on different wounds, the relationship between wound treatment and the cause of systemic adverse events cannot be determined. Thus, the data below are presented with regard to the incidence of adverse events at treatment and control sites (i.e., local events on a per patient basis) and systemic adverse events.

Table 1 Adverse Events with an Incidence of Greater Than 1%

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Pain	2 (10.5%)	0 (0.0%)	1 (5.2%)
Nausea	----------	----------	2 (10.5%)
Redness (total body)	----------	----------	1 (5.2%)
Erythema (non-study site)	----------	----------	1 (5.2%)
Edema (non-study site)	----------	----------	1 (5.2%)
Infection (Upper Respiratory)	----------	----------	1 (5.2%)
Squamous Cell Carcinoma (non-study site)	----------	----------	1 (5.2%)

* *In the U.S. study involving 12 patients, there were 2 control sites per patient (acellular collagen sponge and standard care).*

B. All CCS Treated Patients

The adverse effects observed during clinical evaluations of CCS patients with EB, as well as in other studies include a total of 8 deaths and 71 non-fatal serious adverse events in 186 patients. The non-fatal serious adverse events observed in patients treated with CCS are shown in Table 2. These adverse events were observed in seven clinical studies (including E.B.) and include a broader study population, some with systemic disorders, such as deep partial and full thickness burns. Of the 186 patients for which safety data are available, 82 (44%) had at least one adverse event reported. The adverse events with the highest incidence levels were constipation 26 (13.9%), pain 24 (12.9%), fever 19 (10.2%), pruritis 14 (7.5%) and anemia 13 (6.2%). None of these adverse events (including the non-fatal serious adverse events) were judged by the treating investigators as definitely related to CCS application.

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Hypotension	3
Non-Healing Wound*	3
Infection	3
Autograft (Non-CCS Site)*	3
Renal Failure	2
Pneumothorax*	2

Pneumonia	*2*
Cellulitis	*2*
Leg Clots	*1*
Surgical Interventions:	-
Hip	*2*
Hernia Repair	*1*
Knee	*1*
Periodontal	*1*
Hand	*1*
Thoracotomy	*1*
*Femoral Artery**	*1*
Infarction	*1*
Chest Pain	*1*
CHF	*1*
Minor Stroke	*1*
Seizure Disorder	*1*
Squamous Cell Carcinoma	*1*
Multi System Organ Failure	*1*
*Necrosis to Musculature Around Femoral Artery**	*1*
*Bleed at Femoral Artery**	*1*
TOTAL SERIOUS ADVERSE EVENTS	*71*

** One of these events in each of these categories is related to the control treatment.*

4. HOW COMPOSITE CULTURED SKIN IS USED

Composite Cultured Skin (CCS) is used in patients with mitten hand deformities due to Recessive Dystrophic Epidermolysis Bullosa (RDEB). With standard autograft procedures (i.e., skin grafts and flaps), CCS is used to cover surgical wounds and donor sites created after surgery for release of hand contractures (i.e., "mitten" hand deformities).

The Food and Drug Administration classifies Composite Cultured Skin (CCS) as a HUMANITARIAN USE DEVICE. Federal law restricts this device to sale, distribution and use by or on the order of a physician (or properly licensed practitioner). The effectiveness of this device for use in these indications has not been demonstrated.

Hand Reconstructive Surgery

From 1988 to 1994, a series of 15 operations to release hand contractures using Composite Cultured Skin (CCS) were performed on seven recessive dystrophic epidermolysis bullosa children in Australia. CCS was used on hands in combination with surgical flaps and autografts to cover surgical wounds. CCS was also used to cover donor site wounds in these patients. For additional information please refer to the CCS Package Insert attached to this document.

Because each RDEB patient's hands are affected differently, depending on their age, activity and prior preventive measures, the surgery to correct the "mitten" hand deformity has to be tailored to each patient individually. For example, children below age six may have fused fingers that have not yet progressed to debilitating contractures; older patients are more likely to need release of stiff tissue(s) that prevents useful motion of the fingers even after they are separated. Ask your doctor to describe the procedure for you or your child in more detail.

5. POST-OPERATIVE CARE

For hand reconstruction patients, post-operative dressing changes are usually performed weekly under general anesthesia in the operating room. The number of dressing changes for this type of surgery ranges from 2 to 4 depending on the severity and duration of the contractures. During the 7, 14, and 21-day dressing changes, CCS may be reapplied to any unhealed areas of the hand.

After the first dressing change, a custom-made thermoplastic splint is usually made and fitted by a physiotherapist to maintain fingers in extension and thumb in abduction. Initially the patient uses the splint around the clock. After 6 – 8 weeks, some patients are prescribed an elasticated glove to use over the elasticized bandages applied around each finger. The patient wears the glove during the day and switches back to the splint at night. The ultimate result is heavily dependent upon the patient following a regimen of hand physical therapy under the guidance of a rehabilitation center familiar with EB problems.

Because each RDEB patient's hands are affected differently, depending on their age, activity and the extent of reconstructive surgery, the actual post-operative care and physical therapy program has to be tailored to each patient individually. Ask for written instructions from your physician.

As a patient and parent, you should also be aware of the following instructions:

- Once the area has healed, caution should be taken so as to prevent any unnecessary trauma to the newly healed area, as newly healed skin may be fragile and susceptible to wound breakdown. Patients are instructed to care for the newly healed skin as directed by their physicians.

- Patients are instructed to inspect the newly healed area daily for any of the following signs of breakdown: redness, tenderness, blistering, foul odor, drainage, or a moist, glistening appearance of the area. If any of these signs appear, the patient should notify their physician.

ADDITIONAL INFORMATION & QUESTIONS

Please refer to the Composite Cultured Skin (CCS) Instructions for Use for additional information.

This information was prepared by Ortec International, Inc. It is based on input and guidance from physicians and clinical staff in the United States and Australia. Ortec wishes to thank them for their contributions. However, this information is not a substitute for speaking and

developing a post-operative plan with your physician. We recommend you write down questions for your doctor on a separate piece of paper.

If you should have any problems or questions, or in the event of a product related injury, contact your physician immediately.

If you have any questions regarding the product or need specific information, you can contact:

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